Complete Summary

GUIDELINE TITLE

Breast cancer in limited-resource countries: treatment and allocation of resources.

BIBLIOGRAPHIC SOURCE(S)

Eniu A, Carlson RW, Aziz Z, Bines J, Hortobagyi GN, Bese NS, Love RR, Vikram B, Kurkure A, Anderson BO. Breast cancer in limited-resource countries: treatment and allocation of resources. Breast J 2006 Jan-Feb;12 Suppl 1:S38-53. [85 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 31, 2005, Herceptin (trastuzumab): Healthcare professionals were notified of updated cardiotoxicity information related to use.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Breast Cancer

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Nursing
Obstetrics and Gynecology
Oncology
Radiation Oncology
Radiology
Surgery

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Hospitals
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To develop evidence-based, economically feasible, and culturally appropriate guidelines that can be used in nations with limited health care resources to improve breast cancer early detection and access to care

TARGET POPULATION

Women with breast cancer in limited-resource countries

INTERVENTIONS AND PRACTICES CONSIDERED

Management

1. Consideration of treatment-related issues, including
    - Education of health care professionals, traditional healers, women, governmental agencies, and the public about breast health and about breast cancer detection, diagnosis, and treatment
    - Treatment consideration that respect local cultural, religious, and social factors
2. Staging of tumors

3. Post-treatment surveillance, including history and physical examinations, yearly mammography, and pelvic examination (for women taking tamoxifen)

Treatment*

Local-Regional

1. Surgery
    - Modified radical mastectomy
    - Breast-conserving therapy
    - Sentinel node biopsy
    - Reconstructive surgery
    - Total mastectomy for ipsilateral breast tumor recurrence
2. Radiation
    - Whole-breast irradiation as part of breast-conserving therapy
    - Postmastectomy irradiation of chest wall and regional nodes in high-risk cases
    - Palliative radiation therapy

Systemic

1. Chemotherapy
    - Classical cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)
    - Doxorubicin and cyclophosphamide (AC)
    - Epirubicin and cyclophosphamide (EC)
    - 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC)
    - Taxanes (docetaxel paclitaxel)
    - Growth factors
    - Dose-dense chemotherapy
    - Anthracycline monotherapy or in combination
    - Mono-chemotherapy (capecitabine, Vinorelbine, gemcitabine, carboplatin)
    - Biological therapy (trastuzumab)
2. Endocrine therapy
    - Ovarian ablation
    - Tamoxifen
    - Aromatase inhibitors
    - Luteinizing hormone—releasing hormone (LH-RH) agonists
3. Supportive/palliative therapy
    - Nonopioid and opioid analgesics
    - Bisphosphonates

*Note: Some of these interventions are appropriate or feasible only in countries with maximal or enhanced resources available.

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease-free survival
- Breast cancer morbidity and mortality rates
- Quality of life
- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Breast Health Global Initiative (BHGI) 2005 Guideline panel for early detection and access to care relied on the literature review performed for the 2002 BHGI report and conducted a new MEDLINE search under the subject headings "breast awareness," "clinical breast examination," "breast self-examination," and "mammography," limited to the English language, from 2000 to 2005. They also performed an additional PubMed search under the subject headings "breast cancer," "low-resource countries," and "developing countries," also limited to the English language, from 1990 to 2005.

NUMBER OF SOURCE DOCUMENTS

219

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Source documents were circulated among expert consensus panelists prior to Global Summit review; commentary and review collected and collated in conjunction with preparation of consensus documents.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Consensus Statement Preparation

The observations from the 2002 Breast Health Global Initiative (BHGI) Global Summit (see companion document, "Breast Cancer in Limited-Resource Countries: An Overview of the Breast Health Global Initiative 2005 Guidelines" in "Availability of Companion Documents" field) served as the basis of the 2005 BHGI Global Summit, where specific recommendations were addressed.

The BHGI guidelines were reexamined, revised, and extended at the 2005 BHGI Global Summit. Twelve national and international groups joined the BHGI as collaborating organizations (See Appendix A of the companion document, "Breast Cancer in Limited-Resource Countries: An Overview of the Breast Health Global Initiative 2005 Guidelines" in "Availability of Companion Documents" field). In addition, to obtain input on international guideline development, the BHGI established affiliations with three World Health Organizations programs: the Cancer Control Programme, Health System Policies and Operations, and the Alliance for Health Policy and Systems Research. The 2005 Global Summit brought together more than 60 international experts from 33 countries of all resource levels. The experts had diverse specialties related to breast care and breast cancer: screening, pathology and cytology, surgery, oncology, radiation therapy, health economics, medical ethics, sociology, and advocacy. The treatment and allocation of resources panel was charged with reviewing, updating, and extending the previously published guidelines on this topic and were asked to prepare a consensus statement summarizing the outcome of their work.

Panel cochairs were asked to create a program whereby their expert panel could produce consensus guidelines. The cochairs were responsible for drafting the agenda for the panel's conference day and for organizing and executing the writing of the panel's consensus statement. The panel held one full-day meeting, with a morning session consisting of plenary presentations on topics selected by the cochairs (see Appendix E of the companion document, "Breast Cancer in Limited-Resource Countries: An Overview of the Breast Health Global Initiative 2005 Guidelines" in "Availability of Companion Documents" field) and an afternoon session consisting of discussion and debate among panelists regarding the content of their consensus statement. In addition, to reinforce the aim of the guidelines and to describe the diverse settings in which they might be used, each day began with a presentation by a breast cancer advocate from a limited-resource country to summarize the personal experience of women facing breast cancer in her country.

The panel was also asked to develop checklists for the various interventions. For each intervention, these checklists would describe the strengths, limitations, and necessary resources needed to apply that intervention in the area of early detection and diagnosis. Finally, the panel was asked to identify areas where evidence is lacking and research is needed to better inform future iterations of the guidelines.

The panel's discussion and debate was recorded and transcribed, and the transcript was used as the basis for writing each consensus statement. Panel discussion was directed at creating stratification tables, which list how resources should be allocated based on the definitions of basic, limited, enhanced, and maximal. Panel cochairs coordinated the writing of the statement, sections of which were coauthored by participating panelists.

Individual Statement Preparation

Morning plenary speakers were invited to submit individual statements for publication on their topics along with the consensus statements. In many cases, individual statements were needed to develop and analyze specific topics that were too detailed and focused for inclusion in the consensus statements as a whole, but nonetheless were vital to an understanding of the overall guideline recommendations for limited-resource countries.

In developing this guideline, the panel first reviewed the evidence on the strengths and weaknesses of each cancer therapy and devised checklists of the resources required to deliver that therapy safely and effectively. The resulting overviews of each therapy are presented in Tables 1–4 in the original guideline document. Next, for each of four disease stages—stage I, stage II, locally advanced breast cancer (LABC), and metastatic and recurrent breast cancer—the panel stratified therapies by level after extensive consideration and discussion of the previously described analytic endpoints. The resulting recommendations for resource allocation are presented in Tables 5–8 in the original guideline document and in the "Major Recommendations" field.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Published cost analyses were reviewed in the preparation of this guideline.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consensus Statement Review

Consensus statement drafts were reviewed and edited by all coauthors of each statement. The final draft, including resolution of disagreements among coauthors, was the responsibility of the panel cochairs.

The consensus statements were then compared centrally for internal consistency in stratification by a subset of coauthors. Differences among panel recommendations were reviewed with panel cochairs and language was adopted to minimize the level of perceived inconsistencies. In cases where resources were definitively stratified differently by the consensus panels, the panel recommendations were maintained in the tables, and instead, the nature of the differences are summarized, explained, and discussed in the companion document, "Breast cancer in limited-resource countries: an overview of the Breast Health Global Initiative 2005 Guidelines" (see "Availability of Companion Documents" field).

Individual Statement Selection and Review

In lieu of the standard external peer-review process, submitted individual statements underwent a special internal review process, reflecting the unique structure and goals of the Breast Health Global Initiative (BHGI) program. All individual statement submissions were reviewed by panel cochairs and selected internal BHGI nonauthor reviewers. Individual statements that did not address issues specific to limited-resource countries were referred for journal submission outside of the BHGI guidelines. Some individual statements that developed individual topics of a more limited scope relevant to limited-resource countries were incorporated into guideline consensus articles. Individual statements that were accepted for publication were determined by the cochairs, internal BHGI reviewers, and the BHGI director to have specific merit in support of the consensus guidelines.

After final acceptance, all individual statements were coordinated with the consensus guideline statements for internal referencing as data in one or multiple consensus statements. The combination of consensus and individual statements represents a complete BHGI guideline compendium, which is the final work product of the 2005 Global Summit.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

To encourage a consistent approach to the discussion and the guidelines, the panel was asked to stratify health care resources relevant to their assigned areas into one of four levels (Basic, Limited, Enhanced, and Maximal). Definitions for the levels are provided at the end of the "Major Recommendations" field.

Treatment-Related Issues

Principles of Breast Cancer Treatment

The treatment of localized invasive breast cancer involves an assessment of the clinical and pathologic features of the tumor and of the health status of the patient; the application of therapy aimed at eradicating local disease in the breast, the chest wall, and the regional lymph nodes; the potential application of systemic therapy aimed at eradicating subclinical, micrometastatic disease; and the follow-up of women after treatment for evidence of recurrent disease. Relapsed or metastatic disease is, with few exceptions, incurable; treatment is aimed at controlling symptoms, with the aim of preserving quality of life and prolonging survival.

Early and Accurate Diagnosis

The early and accurate diagnosis of breast cancer is important for optimizing treatment. Compared with the treatment of more advanced breast cancer, the treatment of early breast cancer is less resource-intensive and generally has superior outcomes. Accurate histologic diagnosis is necessary to ensure that women with breast cancer may be given optimal treatment and that healthy

women are not erroneously treated. The availability of resources to provide accurate histologic diagnosis and accurate assessment of prognostic and predictive factors, such as the presence or absence of estrogen receptors (ERs) and progesterone receptors (PRs) in a tumor, is crucial for making decisions regarding systemic therapy and for providing cost-effective breast cancer care. The following guidelines offer approaches for the early detection of breast cancer and the diagnosis of breast cancer when health care resources are limited.

Education

Education of health care professionals, traditional healers, women, governmental agencies, and the public about breast health and about breast cancer detection, diagnosis, and treatment is central to the provision of high-quality breast cancer care.

Access to Breast Cancer Data

The availability of cancer registries is highly desirable. Such registries assist in assessing the effectiveness of breast cancer care in the region of the registry and in identifying areas to which limited resources should be applied to optimize breast cancer care. In the absence of cancer registries, cancer incidence can be approximated using GLOBOCAN data provided by the World Health Organization WHO. However, these estimated statistics cannot be used for monitoring the outcomes of interventions.

Cultural, Religious, and Social Factors

Breast cancer, its diagnosis, and its treatment impact the patient, the patient's family, and society in many ways. Consequently, treatment considerations must respect local cultural, religious, and social factors.

Staging Systems

The use of consistent, reproducible criteria for the staging of breast cancer allows for the comparison of treatments across treatment facilities, the selection of appropriate treatment for the individual patient, and the estimation of overall prognosis. The American Joint Committee on Cancer (AJCC) and the TNM Committee of the International Union Against Cancer (UICC) have both developed Tumor Node Metastasis (TNM)-based tumor staging systems that are similar and compatible. This guideline uses the clinical staging system for breast cancer developed by the AJCC and updated in 2002.

Stage I and II Breast Cancer

Local Treatment

Local treatment of stage I or II disease entails modified radical mastectomy (with postmastectomy radiation therapy in some cases) or breast-conserving surgery followed by radiation therapy.

Modified Radical Mastectomy

Local treatment of stage I and II breast cancer normally requires treatment of the entire breast and the axillary lymph nodes with surgery, radiation therapy, or a combination of these. Modified radical mastectomy (mastectomy plus a level 1 and level 2 axillary dissection) is effective local treatment for breast cancer and uses surgical techniques that are widely available. This procedure is a rapid treatment and is usually associated with a short posttreatment convalescence and limited long-term complications.

Modified radical mastectomy may be performed alone or in association with reconstruction. A number of breast reconstruction techniques are available that differ greatly in the extent of surgery, complication rates, technical difficulty for the surgical team, and recovery. Reconstruction of the breast enhances body image, self-esteem, and psychosocial adjustment for many women, but does not impact the probability of disease recurrence or survival. Unfortunately the cost of breast reconstruction can be prohibitive in countries with limited resources, with costs depending on whether the procedure is performed using implants, myocutaneous flap reconstruction, or a combination of these.

After treatment by mastectomy and adjuvant systemic therapy, there is a substantial risk of local-regional recurrence within the first 1–2 years, particularly in the chest wall, when the ipsilateral axillary lymph nodes are involved by cancer. Postoperative radiation therapy substantially decreases the risk of local-regional recurrence and has also been shown to improve survival among patients with positive lymph nodes.

Breast-Conserving Therapy

An alternative treatment to mastectomy is breast-conserving therapy, that is, breast-conserving surgery (a lumpectomy or a "quadrantectomy") followed by radiation therapy. More specifically, breast-conserving therapy entails complete excision of the tumor in the breast, surgical axillary staging, and radiation therapy to the whole breast and potentially to the regional lymph node-bearing areas. Under appropriate conditions, breast-conserving therapy allows preservation of the breast and provides survival equivalent to that of a modified radical mastectomy. The main benefit of breast-conserving surgery for many women is the preservation of body image, which greatly improves their quality of life.

Breast-conserving therapy requires high-quality breast imaging (mammography and, if available, ultrasound) to ensure that complete excision of the tumor is possible and is achieved, and surgical pathology services to ensure tumor-free margins of excision. If it is not feasible to perform detailed margin assessment because pathology services are unavailable, it may still be reasonable to provide local control with surgery and radiation, if it is possible to create wide (greater than 1.0 cm) margins, using the "quadrantectomy" skin-resecting approach.

Other requirements for breast-conserving therapy include surgical services experienced in achieving a good cosmetic result while achieving negative pathologic margins of excision, support systems to allow for the delivery of radiation therapy over a period of weeks, and the availability of radiation therapy facilities. The radiation therapy facilities should have radiation oncologists and support staff (including technologists and medical physicists), megavoltage radiation teletherapy equipment, a simulator, immobilization devices, and a

planning computer. In addition, the facilities should be geographically accessible to patients and should allow treatment without long delay.

Studies evaluating the use of wide excision of the tumor alone (i.e., without radiation therapy) have demonstrated higher rates of recurrence in the local-regional area, but major differences in survival have not been observed. However, the panel consensus is that patients who can undergo breast-conserving surgery without radiation therapy are the exceptions rather than the rule. In other words, a health care system must be able to provide radiation therapy in order to offer surgery less than modified radical mastectomy for invasive cancer.

Postmastectomy Irradiation of the Chest Wall and Regional Lymph Nodes

The chest wall and regional lymph nodes represent a common site of recurrent disease after modified radical mastectomy. Risk factors for local-regional recurrences include involved axillary lymph nodes, large tumor size, positive margins of resection, and involvement of the skin or chest wall. In North American breast cancer treatment guidelines, postmastectomy radiation therapy is generally recommended for tumors larger than 5 cm in maximum diameter and those with four or more involved axillary lymph nodes, those with positive surgical margins on resection, and those with involvement of the skin or underlying chest wall. The use of postmastectomy chest wall radiation therapy decreases the relative risk of local-regional recurrences in all groups of patients, with the largest absolute risk reduction occurring in those with the highest risk for recurrent chest wall disease. Postmastectomy chest wall and regional lymph node irradiation with a proper technique may also improve overall survival in women with axillary lymph node-positive breast cancer.

There is general agreement that patients with four or more positive axillary nodes should receive radiation therapy after mastectomy, but its role among patients with one to three positive nodes remains controversial. As for breast-conserving therapy, necessary resources include the availability of radiation therapy facilities (equipment and staff), geographic accessibility, access to treatment without long delay, and support systems to allow delivery of radiation therapy over a period of weeks. Recommended doses and schedules for radiation therapy are outlined in an accompanying article (see "Availability of Companion Documents" field).

Systemic Treatment

After primary treatment, a large number of women with initial stage I or II breast cancer will ultimately experience a relapse of their disease and die from it. A number of factors are independently prognostic for recurrence, including the number of involved axillary lymph nodes, tumor size, tumor histologic grade, and tumor hormone receptor status. These factors may be used to estimate a woman's individual risk for recurrence of disease and of death from disease when given local treatment alone. These same factors may also be used to predict the relative and absolute reduction in risk of recurrence and of death from breast cancer that is achieved with the use of systemic chemotherapy or endocrine therapy. The decision-making process regarding the use of systemic therapy thus is strongly influenced by the pathologic characteristics of the tumor, especially tumor size, number of involved axillary lymph nodes, and tumor hormone receptor status. Computer-based models have been developed for estimating the

risks of breast cancer relapse and death, and the benefits from adjuvant therapy in North American populations of women. The applicability of these models to other populations has not been assessed.

The availability of careful pathologic assessment, including the determination of tumor ER and PR content, is central to making decisions about systemic adjuvant therapy. The best current technology for assessing hormone receptor status is with immunohistochemical reactions performed on histologic sections prepared from paraffin-embedded breast tumor tissues that have been fixed in 10% buffered formalin. Across different populations, approximately 55% of breast tumors will stain positive for both ER and PR, 8% will stain positive for ER only, 8% will stain for PR only, and 29–39% of tumors will not stain positive for either receptor.

Endocrine Therapy

Many breast cancers are responsive to a wide variety of endocrine therapies. Benefit from such therapies may be predicted by the presence of ER or PR in the breast cancer. The use of adjuvant endocrine therapy in women with hormone receptor-positive breast cancer substantially reduces the risk of disease recurrence and death. The benefit from endocrine therapy is considerable enough that in the absence of hormone receptor determination (i.e., unknown receptor status), a breast cancer should be considered receptor positive. The most widely used endocrine therapy is the selective estrogen receptor modulator (SERM) tamoxifen. The SERM toremifene is similarly efficacious. Evidence suggests that 5 years of tamoxifen therapy is superior to shorter durations of therapy. Ten years of tamoxifen therapy provided no advantage over 5 years of therapy in two studies of women with lymph node-negative breast cancer.

The benefit of chemotherapy is additive to that achieved with the use of tamoxifen. Therefore the use of both cytotoxic chemotherapy and tamoxifen provides benefits greater than those from either therapy alone. Tamoxifen is associated with toxicity, including hot flashes and a low risk of thromboembolic disease, endometrial carcinoma, and cataracts. In postmenopausal women, tamoxifen appears to maintain bone mineral density. In women with hormone receptor-positive tumors, tamoxifen decreases the risk of second, contralateral breast cancers.

In postmenopausal women, the major source of estrogen is the conversion of adrenally synthesized androgen to estrogens by the aromatase enzyme. This conversion is inhibited by the use of selective aromatase inhibitors. These agents do not adequately suppress estrogen levels in women with functioning ovaries. Selective aromatase inhibitors have been evaluated in postmenopausal women in direct comparison with tamoxifen or in sequence with tamoxifen. Recent evidence from six randomized phase III trials suggests a benefit from the use of aromatase inhibitors in postmenopausal women either alone or sequentially with tamoxifen. All trials have shown improvement in disease-free-survival in favor of the incorporation of an aromatase inhibitor in the treatment of hormone receptor-positive breast cancer in postmenopausal women.

These gains achieved with aromatase inhibitors must be balanced with the substantial costs associated with these agents as well as their different toxicity

profiles. Tamoxifen and the aromatase inhibitors are usually very well tolerated, with few patients stopping treatment due to toxicity. However, tamoxifen causes more uterine bleeding, endometrial cancer, and thromboembolism. Substantial numbers of patients who take aromatase inhibitors experience musculoskeletal symptoms, osteoporosis, and fractures.

The aromatase inhibitors should only be used in postmenopausal women with breast cancers that express ER or PR. Many related questions remain unanswered, including the optimal duration of adjuvant endocrine therapy, the ideal sequence of tamoxifen and aromatase inhibitors, and the long-term toxicity and risks of the aromatase inhibitors. The aromatase inhibitors should not be used in the treatment of invasive breast cancer in women with functioning ovaries.

Ovarian ablation (e.g., surgical oophorectomy or radiation ablation) or suppression (e.g., use of gonadotropin-releasing hormone or luteinizing hormone–releasing hormone [LH-RH] analogs) with or without tamoxifen is an effective endocrine therapy in the treatment of breast cancer in premenopausal women. Early studies of ovarian ablation or suppression in premenopausal women unselected for the hormone receptor status of their breast cancer demonstrated disease-free and overall survival equivalent to those achieved with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy. Recent studies have demonstrated that ovarian ablation plus tamoxifen may be superior to CMF chemotherapy in premenopausal women with hormone receptor-positive breast cancer.

Cytotoxic Chemotherapy

Cytotoxic chemotherapy has an established role in the treatment of invasive breast cancer. It is important that this therapy not be unnecessarily delayed, nor should suboptimal doses or schedules of treatment be given. Policymakers, administrators, providers, and patients must understand that reducing the standard dosage administered or the number of courses given can compromise the benefits of this therapy and that doing so simply to reduce costs is unacceptable.

In women who have undergone local treatment for stage I or II breast cancer, cytotoxic chemotherapy reduces the annual odds of recurrence by approximately 24%. This therapy is beneficial to patients regardless of hormone receptor or axillary lymph node status. The magnitude of risk reduction for recurrence or death achieved with combination chemotherapy decreases with increasing age. The efficacy of cytotoxic chemotherapy in women more than 70 years of age remains uncertain. Both physicians offering this treatment and their patients should understand the degree of risk reduction it may provide. In general, combination chemotherapy is superior to single-agent chemotherapy. As previously noted, the benefits achieved with cytotoxic chemotherapy are additive to those achieved with tamoxifen.

Node-Negative Breast Cancer

Many patients with node-negative breast cancer experience recurrence of their disease. Independent prognostic factors may be used to distinguish women who are more likely to have a recurrence; these factors include age, tumor grade,

histology, and hormone receptor status. HER-2/neu status and angiolymphatic invasion have also been proposed as independent prognostic factors. Thus women with axillary node-negative disease who have a moderate risk of recurrence can experience benefit from chemotherapy. A variety of chemotherapy regimens can be used; four cycles of doxorubicin and cyclophosphamide (AC) or six cycles of CMF are widely used and appropriate regimens in this context. Women who have small, hormone receptor-positive stage I tumors or comorbid conditions and women who are elderly may derive little benefit from the addition of chemotherapy to endocrine therapy.

Node-Positive Breast Cancer

The benefits of adjuvant chemotherapy in patients with node-positive breast cancer have been well established. A number of cytotoxic chemotherapy regimens are effective for treating such disease. In unselected women, anthracycline-containing chemotherapy appears overall to be superior in efficacy to CMF chemotherapy. Classical (oral cyclophosphamide) CMF has proved to be equivalent to anthracycline-based chemotherapy in several clinical trials, and represents an effective and less expensive adjuvant chemotherapy regimen. Although the chemotherapy agents in CMF are less expensive than those in AC, CMF requires more frequent visits and intravenous administrations. Furthermore, patient compliance with the oral cyclophosphamide used in the most effective CMF regimen is not assured.

In the adjuvant setting, the addition of taxanes to anthracycline-based chemotherapy may be superior to anthracycline-based chemotherapy alone. Interpretation of the results of studies of this combined approach is confounded by the potential interaction between endocrine therapy and taxanes. At present, the routine use of taxanes for the treatment of breast cancer in the adjuvant setting is still controversial in women with hormone receptor-positive breast cancer.

Cytotoxic chemotherapy often requires intravenous administration and may be associated with serious and sometimes life-threatening complications. Such therapy must be delivered by an experienced health care team that is familiar with the management of immediate and delayed toxicities of the chemotherapy regimen. In addition, the use of cytotoxic chemotherapy requires the availability of laboratory facilities to monitor white blood cell, red blood cell, and platelet counts; the ability to monitor cardiac function (echocardiography, electrocardiography); pharmacy services to compound the drugs; antiemetics; infusion facilities to administer intravenous chemotherapy; and the availability of medical services to monitor and manage the toxicities of treatment (laboratory facilities, transfusion services for red blood cells and platelets, growth factors, hydration facilities, microbiology laboratories, broad-spectrum antibiotics, and pulmonary and cardiac support systems).

Locally Advanced Breast Cancer

Locally advanced breast cancer (LABC) encompasses breast cancer with a wide range of biological behaviors. It includes cancer with the following features:

- T3 tumors: those larger than 5 cm in greatest diameter

- T4 tumors: those with chest wall involvement, edema, or ulceration of the skin; those with satellite nodules; or inflammatory carcinoma
- N2 nodal status: metastasis in ipsilateral axillary lymph node(s) fixed to surrounding structures or to each other, or metastasis in clinically apparent ipsilateral internal mammary lymph node(s) without axillary lymph node involvement
- N3 nodal status: metastasis in ipsilateral internal mammary lymph node(s) with ipsilateral axillary lymph node involvement, or metastasis in ipsilateral infraclavicular or supraclavicular lymph node(s)

Locally advanced breast cancer represents 50–80% of all breast cancer cases in countries with limited resources. Approximately half of the women die of their disease within 5 years of diagnosis. The treatment of LABC is multidisciplinary, necessitates extensive staging, and requires a combined-modality treatment approach involving surgery, radiation therapy, and systemic therapy. LABC is thus an important health problem that uses substantial resources. Such resources could be used in a more effective way if these cancers were detected at an earlier stage.

The initial management of LABC requires histologic sampling (e.g., core biopsy, incisional biopsy, or skin biopsy) for confirmation of the diagnosis and for determination of hormone receptor status prior to the initiation of neoadjuvant chemotherapy.

Neoadjuvant Chemotherapy

The standard approach to LABC requires initial treatment with anthracycline-based neoadjuvant (primary) chemotherapy for four to eight cycles. Anthracycline-based chemotherapy is preferred over CMF chemotherapy based on indirect evidence from studies of women with axillary node-positive breast cancer or metastatic disease. An adequate dose intensity and total dose of anthracycline should be used and treatment should be given without long delay. CMF chemotherapy is appropriate in women who cannot receive anthracycline-containing chemotherapy because of underlying heart disease.

Patients who are treated with neoadjuvant chemotherapy need to be monitored carefully for evidence of response. Patients with LABC whose tumors respond to primary chemotherapy fare better than those with breast cancers that do not respond to primary chemotherapy. A pathologic complete response to primary chemotherapy predicts better survival. Patients with responding tumors should receive neoadjuvant treatment for up to eight cycles, depending upon the response of the disease and the chemotherapy regimen utilized; the threshold for anthracycline associated cardiac toxicity should not be exceeded. Patients who do not respond after four cycles of optimally dosed anthracyclines generally receive local treatment.

In the neoadjuvant setting, the addition of a sequential taxane after anthracycline-based chemotherapy has been demonstrated to increase the rate of pathologic complete response compared with anthracycline-based chemotherapy alone. However, this improvement did not translate into a survival benefit in the largest of these trials. Therefore the role of the taxanes in primary chemotherapy for inoperable LABC remains to be defined.

Recent evidence suggests that neoadjuvant endocrine therapy may be beneficial in postmenopausal patients with hormone receptor-positive disease. Patients who are not candidates for any chemotherapy can be initially managed with endocrine therapy (an aromatase inhibitor or tamoxifen in postmenopausal women, or tamoxifen in premenopausal women) and then receive local treatment. Although all of the trials suggest a benefit in favor of aromatase inhibitors over tamoxifen, there are no long-term follow-up or survival data available. Therefore the neoadjuvant use of aromatase inhibitors in LABC remains investigational.

Local Treatment

Optimal control of LABC requires, when feasible, local treatment with both surgery and radiation therapy.

Surgery

After an initial course of neoadjuvant chemotherapy, the use of surgery is appropriate. Most patients with LABC will require a modified radical mastectomy, a procedure that remains the standard surgical treatment for operable locally advanced disease. The role of breast-conserving surgery in LABC is unclear and the subject of research. Selected patients may be treated with wide local excision followed by whole-breast and regional lymph node irradiation. Because the majority of patients in developing countries present with locally advanced disease, including positive lymph nodes, treatment with mastectomy without postoperative irradiation of the chest wall and regional lymph nodes would generally be insufficient in this setting.

Radiation Therapy

The results of randomized trials and data extrapolated from trials involving women with node-positive disease support the use of local-regional radiation therapy in patients with LABC who are treated with mastectomy. This therapy should be delivered to the chest wall and to the supraclavicular and axillary nodes. The recommended dose of radiation is 50 Gy in 25 fractions or equivalent. The role of internal mammary lymph node irradiation is unclear.

In patients in whom mastectomy is not possible after neoadjuvant chemotherapy, the use of whole-breast and regional lymph node irradiation alone is appropriate. Patients who are treated with radiation therapy without surgery should be given tumoricidal doses to areas of bulk disease (60–66 Gy in 30–33 fractions or equivalent).

Systemic Treatment after Local Treatment

After local treatment, systemic treatment may entail chemotherapy and endocrine therapy.

Chemotherapy

After local treatment, most patients should be treated with additional chemotherapy. A recently reported study showed a trend toward improved

relapse-free and overall survival even in those patients with LABC who had a poor response to anthracycline-based neoadjuvant chemotherapy when given a non-cross-resistant regimen after surgery.

Endocrine Therapy

The panel's recommendations for adjuvant endocrine therapy of LABC are the same as those for stage I and II breast cancer. After completion of chemotherapy, patients with LABC and hormone receptor-positive tumors should receive adjuvant endocrine therapy. The role of aromatase inhibitors in postmenopausal women with hormone receptor-positive LABC continues to be defined, although their activity should be substantial based on the results achieved with the use of adjuvant or sequential aromatase inhibitors in early stage breast cancer.

Metastatic (Stage IV) or Recurrent Breast Cancer

Patients with detectable metastatic or recurrent breast cancer have, with rare exceptions, incurable disease. The treatment of their breast cancer is based on prognostic and predictive factors and how the available therapies are expected to impact both quality of life and overall survival.

Local-Regional Treatment

For patients with metastasis confined to a single site, local treatment with surgery, radiation therapy, or both is appropriate. In women who have undergone breast-conserving therapy and who experience an ipsilateral in-breast recurrence of their disease, the use of total mastectomy is appropriate treatment. In addition, for those with disease causing or likely to cause a significant catastrophe (e.g., spinal cord compression or central nervous system metastasis), local treatment with surgery or radiation therapy is necessary. Radiotherapy can be very effective for symptomatic relief. Studies have shown, for instance, that after a very short (1–2 days) course of radiotherapy, many patients with painful metastases remain pain free for a considerable proportion of their remaining lives. For the majority of patients who have more than localized disease, systemic treatment is necessary.

Systemic Treatment

Despite advances in primary and adjuvant therapy, metastatic breast cancer is essentially incurable with standard treatment, and the median survival of patients with metastatic breast cancer is approximately 2 years. Systemic treatment in most patients extends survival, but only modestly. The focus of treatment is therefore mainly palliation and improvement of quality of life. The goal is to reduce disease-related symptoms, with minimum treatment-related toxicity.

If the patient has indolent disease, no impending visceral crises, and hormone receptor-positive disease, a trial of endocrine therapy should be given. In patients with an impending visceral crisis or with receptor-negative disease, cytotoxic chemotherapy is preferred, as it is more likely to produce a response. Trials comparing combination chemotherapy with single-agent therapy have shown higher rates of response and longer times to first disease progression with the

combination, but with greater overall toxicity and with survival that is not different from that with the use of sequential single-agent therapy. A number of active cytotoxic agents can be used, including anthracyclines, taxanes, capecitabine, vinorelbine, cyclophosphamide, methotrexate, and gemcitabine. The choice of drugs depends on financial considerations, preferences regarding the route and schedule of administration, and toxicity.

Surveillance after Treatment of Stage I, II, or III Breast Cancer

After the treatment of stage I, II, or III breast cancer, women remain at risk for the development of recurrent disease for many years. The post-treatment surveillance of women for a recurrence includes history and physical examinations at increasing time intervals in conjunction with yearly mammography evaluation and, in women taking tamoxifen, pelvic examination. The use of surveillance chest radiographs, ultrasound, computed tomography, and blood chemistries has not been demonstrated to substantially aid the diagnosis of recurrent disease, nor has it been demonstrated to enhance overall survival.

Summary of Recommendations

The following tables summarize some of the recommendations made by the panel.

Table. Treatment and Allocation of Resources: Stage I Breast Cancer

Level of Resources	Local-regional Treatment		Systemic Treatment (Adjuvant)	
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy
Basic	Modified radical mastectomy			Ovarian ablation Tamoxifen
Limited	Breast-conserving therapy[a]	Breast-conserving whole-breast irradiation as part of breast conserving therapy	Classical CMF[b]	
		Postmastectomy irradiation of the chest wall and regional nodes for high-risk cases	AC, EC, or FAC[b]	
Enhanced			Taxanes	Aromatase inhibitors LH-RH agonists
Maximal	Sentinel node biopsy Reconstructive surgery		Growth factors Dose-dense chemotherapy	

[a]Breast-conserving therapy requires mammography and reporting of margin status.

[b]Requires blood chemistry profile and complete blood count (CBC) testing.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.

Table. Treatment and Allocation of Resources: Stage II Breast Cancer

Level of Resources	Local-regional Treatment		Systemic Treatment (Adjuvant)	
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy
Basic	Modified radical mastectomy	—[a]	Classical CMF[b] AC, EC, or FAC[b]	Ovarian ablation Tamoxifen
Limited	Breast-conserving therapy[c]	Breast-conserving whole-breast irradiation as part of breast conserving therapy Postmastectomy irradiation of the chest wall and regional nodes for high-risk cases		
Enhanced			Taxanes	Aromatase inhibitors LH-RH agonists
Maximal	Sentinel node biopsy Reconstructive surgery		Growth factors Dose-dense chemotherapy	

[a]Chest wall and regional lymph node irradiation substantially decrease the risk of postmastectomy local recurrence. If available, it should be used as a basic-level resource.

[b]Requires blood chemistry profile and complete blood count (CBC) testing.

[c]Breast-conserving therapy requires mammography and reporting of margin status.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.

Table. Treatment and Allocation of Resources: Locally Advanced Breast Cancer

Level of Resources	Local-regional Treatment		Systemic Treatment (Adjuvant)	
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy
Basic	Modified radical mastectomy		Neoadjuvant AC, FAC, or classical CMF[a]	Ovarian ablation Tamoxifen
Limited		Postmastectomy irradiation of the chest wall and regional nodes		
Enhanced	Breast-conserving therapy[b]	Breast-conserving whole-breast irradiation	Taxanes	Aromatase inhibitors LH-RH agonists
Maximal	Reconstructive surgery		Growth factors Dose-dense chemotherapy	

[a]Requires blood chemistry profile and complete blood count (CBC) testing.

[b]Breast-conserving therapy requires mammography and reporting of margin status.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.

Table. Treatment and Allocation of Resources: Metastatic (Stage IV) and Recurrent Breast Cancer

Level of Resources	Local-regional Treatment		Systemic Treatment (Adjuvant)		
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Supportive and Palliative Therapy
Basic	Total mastectomy for ipsilateral breast tumor recurrence[a]			Ovarian ablation Tamoxifen	Nonopioid and opioid analgesics
Limited		Palliative radiation therapy	Classical CMFb Anthracycline monotherapy or in combination[b]		
Enhanced			Taxanes Capecitabine	Aromatase inhibitors	Bisphosphonates

Level of Resources	Local-regional Treatment		Systemic Treatment (Adjuvant)		
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Supportive and Palliative Therapy
			Trastuzumab		
Maximal			Growth factors Vinorelbine Gemcitabine Carboplatin	Fulvestrant	

[a]Required resources are the same as those for modified radical mastectomy.

[b]Requires blood chemistry profile and complete blood count (CBC) testing.

CMF, cyclophosphamide, methotrexate, and 5-fluorouracil

See Tables 1-4 in the original guideline document for overviews of the strengths and weaknesses of and resources required for each recommended cancer therapy.

Resource Stratification Definitions

Basic level: Core resources or fundamental services absolutely necessary for any breast health care system to function. By definition, a health care system lacking any basic-level resource would be unable to provide breast cancer care to its patient population. Basic-level services are typically applied in a single clinical interaction.

Limited level: Second-tier resources or services that produce major improvements in outcome, such as increased survival, but which are attainable with limited financial means and modest infrastructure. Limited-level services may involve single or multiple clinical interactions.

Enhanced level: Third-tier resources or services that are optional but important. Enhanced-level resources may produce minor improvements in outcome but increase the number and quality of therapeutic options and patient choice.

Maximal level: High-level resources or services that may be used in some high-resource countries, but nonetheless should be considered lower priority than those in the basic, limited, or enhanced categories on the basis of cost or impracticality for limited-resource environments. In order to be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved breast cancer morbidity and mortality in limited-resource countries

See Tables 1-4 in the original guideline document for overviews of specific benefits of modified radical mastectomy and breast-conserving therapy, postmastectomy radiation therapy, adjuvant endocrine therapy, and adjuvant cytotoxic chemotherapy.

POTENTIAL HARMS

See Tables 1-4 in the original guideline document for overviews of the specific weaknesses (including adverse effects) of modified radical mastectomy and breast-conserving therapy, postmastectomy radiation therapy, adjuvant endocrine therapy, and adjuvant cytotoxic chemotherapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Four large, multicenter, randomized trials are testing trastuzumab as an addition to the adjuvant treatment of breast cancer patients with overexpression or amplification of HER-2/neu. Since the panel meeting in January 2005, the initial results of three of the trials have been presented. The first interim analysis of the fourth trial (Breast Cancer International Research Group [BCIRG] 006) was completed and will be presented at the European Conference on Clinical Oncology meeting in November 2005. These data were not available for analysis during the panel meeting, and in view of the high costs required for testing and treatment, recommendations concerning the use of trastuzumab will be discussed and included in a future version of this article.
- For further discussion and comments on the integration of recommendations for treatment and the allocation of resources with the conclusions from other panels (Early Detection and Access to Care, Diagnosis and Pathology, and Health Care Systems and Public Policy) see the companion document, "Breast cancer in limited resource countries: an overview of the breast health global initiative 2005 guidelines" (see "Availability of Companion Documents" field). Selected areas are identified where disagreement exists among the panels regarding stratification levels for resources.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

See the original guideline document and companion document, "Breast Cancer in Limited-Resource Countries: Health Care Systems and Public Policy" (see "Availability of Companion Documents" field) for implementation strategies.

IMPLEMENTATION TOOLS

Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Eniu A, Carlson RW, Aziz Z, Bines J, Hortobagyi GN, Bese NS, Love RR, Vikram B, Kurkure A, Anderson BO. Breast cancer in limited-resource countries: treatment and allocation of resources. Breast J 2006 Jan-Feb;12 Suppl 1:S38-53. [85 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

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Fred Hutchinson Cancer Research Center
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GUIDELINE COMMITTEE

Global Summit Treatment and Allocation of Resources Panel

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Center Web site.

Print copies: Available from Alexandru Eniu, MD, Department of Breast Tumors (Oncology), Cancer Institute I. Chiricuta, Republicii 34-36, 3400 Cluj-Napoca, Romania; E-mail: aleniu@iocn.ro.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Breast cancer in limited resource countries: an overview of the breast health global initiative 2005 guidelines. Breast J 2006 Jan-Feb;12 Suppl 1:S3-15. Available in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Center Web site.
- Breast cancer in limited-resource countries: health care systems and public policy. Breast J 2006 Jan-Feb;12 Suppl 1:S54-69. Available in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Center Web site.
- Radiotherapy for breast cancer in countries with limited resources: program implementation and evidence-based recommendations. Breast J 2006 Jan-Feb;12 Suppl 1:S-96-102. Available in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Center Web site.
- The Breast Health Global Initiative (BHGI) resource-stratified matrix guidelines. Breast J 2006 Jan-Feb;12 Suppl 1:S117-20. Available in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Center Web site.

Print copies: Available from Benjamin O. Anderson, MD, Department of Surgery, Box 356410, University of Washington, Seattle, WA 98195, USA, or e-mail: banderso@u.washington.edu.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on July 28, 2006. The information was verified by the guideline developer on August 28, 2006.

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